

Frequency and risk factors of ulcerative colitis associated colorectal cancer referral center experience in non-endemic area

 Yavuz Çağır¹,  İlhami Yüksel^{1,2}

¹Department of Gastroenterology, Ankara Bilkent City Hospital, Ankara, Türkiye

²Department of Gastroenterology, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Türkiye

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ABSTRACT

Aims: The incidence of colorectal cancer (CRC) in ulcerative colitis (UC) patients varies across different geographical regions, with limited data available from non-endemic areas for sporadic CRC. This study aimed to evaluate the CRC rates and risk factors in UC patients in a non-endemic region for sporadic CRC.

Methods: A retrospective cohort study was conducted on UC patients who had at least 6 months of follow-up between June 1993 and February 2023 at a tertiary referral center in Turkey. Risk factors for CRC development were assessed, including age at UC onset, disease duration, extent of colitis, family history of CRC, and treatment response.

Results: A total of 875 UC patients were included in the study. The median age at diagnosis was 38 years, and the median follow-up period was 8.16 years. Of these patients, 133 (15.2%) had proctitis, 426 (48.7%) had left-sided colitis, and 316 (36.1%) had extensive colitis. CRC was histologically diagnosed in 5 (0.6%) UC patients, with a median UC onset age of 29.4 years and a total disease duration of 18 years. The median age at CRC diagnosis was 46 years. Three patients had extensive colitis, while two had left-sided colitis. Three patients had steroid dependence, two had thiopurine resistance, and one was biologic treatment-resistant. All UC-related CRC patients had persistent mild to moderate disease activity on colonoscopy during follow-up.

Conclusion: The low incidence of UC-associated CRC in non-endemic areas may be associated with some environmental and racial factors specific to the region.

Keywords: Colorectal cancer, ulcerative colitis, non-endemic area

MAIN POINTS

- The study showed a strong relationship between disease duration and CRC risk, with patients who developed colorectal cancer having a median overall disease duration of 18 years.
- Over a 30-year period, among 875 UC patients, resulting in a total incidence of CRC related to UC of 0.6%.
- The incidence of CRC linked to UC in our study was lower than that reported in earlier research.
- As current guidelines advice, initiating screening colonoscopy 8–10 years after the initial diagnosis in UC patients with more than one-third of the colon affected appears to be an appropriate approach in non-endemic areas.

INTRODUCTION

Ulcerative colitis (UC), an inflammatory colorectal disease, is characterized by a relapsing and remitting nature.¹ UC is associated with an elevated risk of colorectal cancer (CRC), particularly in patients with longer disease duration, extensive colitis, family history of CRC, concurrent primary

sclerosing cholangitis, and younger age at diagnosis.²⁻⁵ Compared to sporadic CRC, UC-associated CRC is typically diagnosed 15-20 years earlier.⁶ In patients with chronic UC, CRC is a significant contributor to morbidity and mortality. Recent studies have documented an increased risk of CRC development in UC patients.⁷

CRC ranks as the third most diagnosed cancer in males and the second in females.^{8,9} Compared to the general population, pancolitis is associated with a 5-to-15-fold increased risk of CRC, while left-sided colitis is associated with an approximately threefold relative risk. In contrast, the risk does not appear to be significantly elevated in proctitis or proctosigmoiditis alone.^{10,11} The estimated incidence of colon cancer is approximately 0.5% per year for patients with disease duration between 10 and 20 years, increasing to 1% per year thereafter. The risk of colon cancer begins to rise approximately 8 to 10 years after the initial diagnosis of pancolitis and 15 to 20 years for left-sided colitis. The probability of developing cancer increases with disease

Corresponding Author: Yavuz Çağır, yvzcgr@hotmail.com



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duration and active inflammation, reaching as high as 30% in patients with pancolitis by the fourth decade of disease.¹²⁻¹⁴

The reduced rate of CRC in UC patients is primarily attributed to effective colonoscopic surveillance programs and aggressive control of disease activity through medical therapy. Colonic surveillance is recommended for UC patients to prevent the development of CRC.¹⁵ Current guidelines advocate initiating screening colonoscopy with random biopsies every 10 cm of the intestine 8–10 years after the initial diagnosis in UC patients with more than one-third of the colon affected.² The potential association between clinical factors and CRC incidence in UC is not well understood, and there is a lack of knowledge regarding the risk factors and clinical characteristics of UC-associated CRC patients.

The varying rates reported worldwide demonstrate how factors such as geographic location, genetics, and environmental variables can influence the risk of CRC. Asians have a distinct genetic makeup for UC compared to Caucasians, which may impact the risk of disease development, including colon cancer. This study aimed to determine the risk factors and frequency of CRC development in long-term follow-up of UC patients in the Turkish population.

METHODS

Ethics

The study was conducted with the permission of Ankara Bilkent City Hospital Scientific Researches Ethics Committee (Date: 25.01.2023, Decision No: E1/23/3219). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Design and Patient Population

We conducted a retrospective cohort study of UC patients who received care at a tertiary referral center between June 1993 and February 2023. The inclusion criteria were: (1) a confirmed diagnosis of UC, (2) age ≥ 18 years at the time of diagnosis, (3) regular follow-up at our department, and (4) a minimum follow-up duration of 6 months. Patients with missing data or those who had less than six months of follow-up were excluded from the study.

Data Collection and Outcome Measures

Data were retrospectively collected from electronic medical records and the national health system. The information gathered included demographics (age, gender), laboratory variables (hemoglobin, C-reactive protein, albumin), medical and surgical history, treatments (mesalazine, steroids, thiopurines, biological therapies), duration from UC onset to CRC diagnosis, endoscopic findings, and partial Mayo scores. Smoking habits were assessed at the time of UC diagnosis and noted in the patient's chart at the final visit. Patients were classified as current smokers, ex-smokers, or non-smokers. Family history of UC or CRC was also evaluated. The extent of the disease was determined using the Montreal classification (proctitis, left-sided colitis, or extensive colitis). Extraintestinal manifestations that developed at diagnosis and during follow-up were recorded. The primary outcome measure was the development of histologically confirmed adenocarcinoma during the follow-up period. The diagnosis

of CRC was confirmed by histopathological examination of biopsy specimens obtained during colonoscopy or surgical resection.

Statistical Analysis

Statistical analysis was performed using SPSS 25.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were described using median and interquartile range (IQR), while categorical variables were expressed as numbers (n) and percentages (%). Patients were stratified based on the duration of the disease (<10 years, 10–19 years, 20–29 years, or ≥ 30 years) and the extent of the disease (proctitis, left-sided colitis, or extensive colitis). Baseline characteristics, including hemoglobin, CRP, albumin, and partial Mayo scores, were reported. The demographic and clinical variables of patients who developed CRC were analyzed separately. Comparisons between the group that developed CRC and the group that did not were performed using appropriate statistical tests, although no statistical differences were observed.

RESULTS

Patient Characteristics

During the study period, 991 UC patients were followed, of which 116 were excluded due to missing data and a short follow-up period. The final study population comprised 875 UC patients, with 547 (62.5%) being male. The median age at diagnosis was 38 years (IQR: 28–49), and the median follow-up duration was 8.16 years (IQR: 4.16–13.5). The disease duration was categorized as follows: <10 years, 532 (60.8%); 10–19 years, 246 (28.1%); 20–29 years, 79 (9%); and ≥ 30 years, 18 (2.1%). Regarding disease extent, 133 (15.2%) patients had proctitis, 426 (48.7%) had left-sided colitis, and 316 (36.1%) had extensive colitis (**Table 1**). The most commonly used medication was mesalazine (843 patients, 96.3%), followed by steroids (356, 40.7%), thiopurines (242, 27.7%), and biological therapies (144, 16.5%). Peripheral arthralgia was the most prevalent extraintestinal manifestation, affecting 174 (19.9%) patients, while primary sclerosing cholangitis was found in 11 (1.3%) patients. At baseline, the median hemoglobin level was 13.7 g/dl, median CRP was 4.45 mg/L (IQR: 1.45–10.27), median albumin was 4.5 g/dl (IQR: 4.2–4.7), and the median partial Mayo score was 6 (IQR: 5–7) (**Table 1**).

Colorectal Cancer Incidence and Patient Characteristics

During the study period, 5 (0.6%) histologically confirmed adenocarcinomas were detected. Among the patients who developed CRC, four were male. The median age at onset of UC was 29.4 years (IQR: 17–43), and the median total disease duration was 18 years (IQR: 4.8–28.5). The median age at CRC diagnosis was 46 years (IQR: 34.5–54.5) (**Table 2**). Three patients were nonsmokers, while the remaining two were former smokers. One patient had a family history of colon cancer.

Regarding disease extent, three patients had extensive colitis, and two had left-sided involvement. Three patients had steroid dependence, two had thiopurine resistance, and one had a biologically resistant condition. One patient had poor compliance with medical treatment. All UC-related CRC

Table 1. Demographic characteristics of patients with ulcerative colitis

Ulcerative colitis (n=875)	
Age at onset of UC (years)	38 (28-49)
Total disease duration (years)	8.16 (4.16-13.5)
Disease duration	
<10 years	532 (60.8%)
10-19 years	246 (28.1%)
20-29 years	79 (9%)
≥30 years	18 (2.1%)
Colorectal cancer	5 (0.6%)
Duration from onset of UC to colorectal cancer (years)	8.41 (4.2-28.37)
Gender, male	547 (62.5%)
Smoking (current/ex/none)	105 (12%)/294 (33.6%)/476 (54.4%)
Family history of UC	103 (11.8%)
Appendectomy	16 (1.8%)
UC (disease extension)	
Proctitis	133 (15.2%)
Left-sided colitis	426 (48.7%)
Extensive colitis	316 (36.1%)
Extra-intestinal manifestations	
Peripheral arthralgia	174 (19.9%)
Peripheral arthritis	36 (4.1%)
Ankylosing spondylitis	33 (3.8%)
Sacroiliitis	11 (1.3%)
Erythema nodosum	9 (1%)
Pyoderma gangrenosum	2 (0.2%)
Aphthous ulcer	119 (13.6%)
Uveitis	11 (1.3%)
Episcleritis	2 (0.2%)
Primary sclerosing cholangitis	11 (1.3%)
Medication (conventional)	
Mesalazine	843 (96.3%)
Sulfasalazine	68 (7.8%)
Steroids	356 (40.7%)
Thiopurine	242 (27.7%)
Biological therapy	144 (16.5%)
Baseline CRP (mg/L)	4.45 (1.45-10.27)
Baseline HB (g/dl)	13.7 (12.2-15)
Baseline albumin (g/dl)	4.5 (4.2-4.7)
Baseline partial MAYO score	6 (5-7)

Variables are reported as median (1st quartile-3rd quartile) or frequency (%). UC: Ulcerative colitis, IQR: Interquartile range, CRP: C-reactive protein, HB: Hemoglobin

patients had persistent mild to moderate disease activity on colonoscopy (**Table 3**). CRC developed in three patients with a disease duration of less than 9 years. One patient (aged 34) developed CRC after two years of having pancolitis. Another patient, also aged 34, had left-sided involvement and developed CRC.

Several factors were proportionally higher in the group that developed CRC, including male gender, younger age at UC onset, longer total disease duration, extensive colitis, steroid dependency, thiopurine resistance, and biologic agent resistance. However, no statistically significant differences were observed between the CRC and non-CRC groups for these variables (**Table 4**).

DISCUSSION

This study, conducted at a tertiary center in Turkey, included a long-term follow-up of UC patients and reported a low incidence rate of CRC. Over a 30-year period, five cases of CRC were identified among 875 UC patients, resulting in a total incidence of CRC related to UC of 0.6%. This finding emphasizes the importance of performing surveillance colonoscopies to detect dysplasia early and prevent the

development of CRC. The present study demonstrated a strong relationship between disease duration and CRC risk, with patients who developed CRC having a median overall disease duration of 18 years. This observation is consistent with the hypothesis that chronic inflammation and mucosal damage secondary to prolonged disease activity trigger the neoplastic process.¹⁶

Chronic inflammation is known to release cytokines that are involved in various stages of cancer development, including angiogenesis, metastasis, tumor promotion, and initiation.^{17,18} The current study supports this concept, as steroid dependency, resistance to immunomodulators, and biological agents, which are indicators of chronic inflammation, were more prevalent in the patient group that developed CRC.

Previous studies have identified several factors that increase the risk of CRC in UC patients, including the presence of pancolitis, prolonged disease duration, moderate-to-severe or persistent inflammatory activity, smoking, and age.^{19,20} In line with these findings, the current study observed that male gender, younger age at UC onset, longer total disease duration, and extensive colitis were more common among patients who developed CRC. However, no statistically significant differences were found between the CRC and non-CRC groups, possibly due to the relatively low number of patients who developed CRC in this cohort.

Based on previous studies, UC patients have a cumulative risk of developing CRC ranging from 2% to 10% over a ten-year period.⁷ CRC is a major cause of mortality and morbidity among UC patients, accounting for 10% to 15% of deaths.²¹ Several confirmed risk factors for colitis-associated CRC include concomitant primary sclerosing cholangitis, disease duration and severity, the severity of colitis, and a family history of CRC.⁷

The risk of developing CRC varies depending on the extent of the disease. Patients with pancolitis have the highest risk, while those with left-sided colitis have a moderate risk.⁷ Disease extent and duration are widely recognized as risk factors for CRC in UC patients. Most malignancies originate in extensive colitis, and proctitis is generally considered to carry little to no increased risk, while left-sided colitis has an intermediate risk of cancer. In elderly-onset UC, a less aggressive phenotype with primarily left-sided colitis and less extensive colitis has been observed.^{22,23} Our study findings are consistent with the literature, as two patients with UC-CRC had left-sided UC, and three patients had extensive UC. According to meta-analyses that included IBD patients of all ages, the age at UC diagnosis in adults does not affect the relative risk of CRC.²⁴

Previous Turkish studies reported a prevalence rate of UC-associated CRC of 1.1% between 1994 and 2008²⁵ and 0.7% between 1993–2016.²⁶ In our study, CRC affected 0.6% of the incident UC population between 1993 and 2023. The incidence of CRC linked to UC in our study was lower than that reported in earlier research. This finding is in line with the recent trend of decreasing CRC prevalence in UC patients, although it remains a significant concern.²⁷ As current guidelines advocate, initiating screening colonoscopy 8–10 years after the initial diagnosis in UC patients with more than

Table 2. Characteristic features of ulcerative colitis patients with colorectal cancer

	1. case	2. case	3. case	4. case	5. case	Total
Age at onset of UC (years)	43	32	28	27	17	29.4 (17-43)
Total disease duration (years)	19.5	4.8	28.5	9.3	28.2	18 (4.8-28.5)
Gender	M	M	F	M	M	
Smokers (ex/none)	Ex	None	None	None	Ex	
Family history of IBD	-	-	-	+	-	
Age at onset of colon cancer (years)	51.7	34.5	57.3	33.6	46.2	46 (34.5-54.5)
Duration from onset of UC to colorectal cancer (years)	8.41	2	28.5	6.41	28.25	8.41 (4.2-28.37)
Family history of colorectal cancer (yes +/-no -)	-	-	-	+	-	
Uncontrolled disease activity	+	+	+	+	+	
UC (disease extension)						
Left-sided colitis	-	-	-	+	+	
Extensive colitis	+	+	+	-	-	
Extra-intestinal manifestations	-	-	+	-	-	
Medication (conventional)						
Mesalazine oral	+	+	+	+	+	
Mesalazine enema	-	-	+	+	-	
Mesalazine suppository	-	-	-	+	-	
Sulfasalazine	-	-	-	-	+	
Budesonide	-	-	-	+	-	
Steroids	-	+	+	+	-	
Thiopurine	+	+	+	+	-	
Steroid dependence/resistance	-	+/-	+/+	+/+	-	
Thiopurine resistance	-	-	-	+	-	
Biological therapy	-	-	ADA-VEDO	-	-	
Biologic resistance						
Adalimumab	-	-	+	-	-	
Baseline CRP (mg/L)	8	50	32	25.6	1.4	25.6 (4.68-41)
Baseline HB (g/dl)	12.8	11.2	10.1	15	11.9	11.9 (11.2-12.8)
Baseline albumin (g/dl)	4	2.8	4	4.9	4.3	4 (4-4.3)
Baseline endoscopic MAYO	2	3	3	3	3	2.8 (2-3)
Baseline partial MAYO score	5	7	8	7	8	7 (7-8)
Baseline total MAYO score	6	11	10	10	12	10 (10-11)

Variables are reported as median (1st quartile-3rd quartile) or frequency (%) UC: Ulcerative colitis, IBD: Inflammatory bowel disease, CRP: C-reactive protein, HB: Hemoglobin. (+=Yes) and (-=No). M: Male, F: Female, ADA: Adalimumab, VEDO: Vedolizumab

Table 3. Colorectal cancer risk factors in patients with ulcerative colitis

	CRC (+) (n=5)	CRC (-) (n=737)	p-value
Age at onset of UC (years)	28 (22-37.5)	37 (27-49)	0.129
Total disease duration (years)	19.5 (7.08-28.38)	8.5 (4.25-14.17)	0.074
Gender, male	5 (100)	459 (62.3)	0.163
UC (disease extension)			0.656
Left-sided colitis	2 (40)	424 (57.5)	
Extensive colitis	3 (60)	313 (42.5)	
Extra-intestinal manifestations	1 (20)	258 (35)	0.663
Steroid dependence	3 (60)	225 (30.5)	0.172
IM resistance (thiopurine, MTX)	1 (20)	89 (12.1)	0.477
Biological resistance	1 (20)	54 (7.3)	0.320
Baseline partial MAYO score	7 (6-8)	6 (5-7)	0.111
Baseline total MAYO score	10 (8-11.5)	8 (7-10)	0.148

UC: Ulcerative colitis, CRC: Colorectal cancer, IM: Immunomodulatory, MTX: Methotrexate

Table 4. Univariate and multiple variate logistic regression analysis of predictors of colorectal cancer in ulcerative colitis

	Univariate analysis				Multiple variate analysis			
	OR	95% CI Lower	95% CI Upper	p	OR	95% CI Lower	95% CI Upper	p
Age at onset of UC (years)	0.943	0.872	1.021	0.150	0.951	0.862	1.048	0.309
Total disease duration (years)	1.087	1.006	1.174	0.034	1.072	0.981	1.172	0.125
Gender, male	>100	0	-	0.994	-	-	-	-
UC (disease extension)								
Left-sided colitis	1	-	-	-	-	-	-	-
Extensive colitis	2.032	0.388	12.233	0.439	-	-	-	-
Extra-intestinal manifestations	0.464	0.052	4.174	0.493	-	-	-	-
Steroid dependence	3.413	0.566	20.568	0.180	0.386	0.022	6.674	0.513
IM resistance (thiopurine, MTX)	1.820	0.201	16.468	0.594	-	-	-	-
Biological resistance	3.162	0.347	28.788	0.307	-	-	-	-
Baseline partial MAYO score	1.654	0.830	3.294	0.152	0.324	0.040	2.646	0.293
Baseline total MAYO score	1.355	0.860	2.135	0.191	3.173	0.803	12.535	0.100

UC: Ulcerative colitis, IM: Immunomodulatory, MTX: Methotrexate

one-third of the colon affected appears to be an appropriate approach in non-endemic areas.¹

5-ASA compounds, the first-choice drugs in the treatment of UC, are also used at a dose of 2 g/day for CRC prophylaxis. In our clinical management of UC, we maintain prophylactic 5-ASA even in patients with mucosal healing, which may contribute to the low CRC rate observed in our study. In our practice, we promptly initiated immunomodulator or biological therapy for moderate-to-severe UC when required. Immunomodulators and biological agents have been associated with increased mucosal healing, which may have contributed to the decreased incidence of CRC in our study population.

The incidence of CRC in UC patients varies according to geographical location. A population-based cohort study of 96,447 UC patients in Denmark and Sweden between 1969 and 2017 reported a CRC incidence of 1.23%.¹¹ Another study by Bernstein et al.²⁸ in Canada found an even higher CRC incidence of 1.8% among 19,665 UC patients followed for 13 years. In contrast, our study demonstrated a lower risk of CRC in UC patients. There may be two logical explanations for the lower risk of CRC in UC patients in our study compared to the aforementioned studies. First, considering the follow-up dates of the above studies, immunomodulators and biologic agents, which have been shown to effectively suppress mucosal inflammation, were likely not used in the patients during their follow-up periods. Second, geographical differences, such as genetics, environmental factors, and nutritional habits, may contribute to the observed variation in CRC incidence.

The incidence of UC in Turkey is lower than in North-West Europe but similar to that in the Middle East. The low incidence rates of UC in Turkey, which are comparable to those in Western European countries, may be attributed to genetic factors, lifestyle, environmental variables, and even climate. Turkey, with a population of more than 80 million people, is predominantly young and has characteristics of both the east and west. However, CRC rates due to UC in Turkey have been observed to be more similar to those in the eastern region, rather than representing a transition between these regions. In our study, only five UC patients with CRC (0.6%) were identified. This low rate can be partially explained by the overall low incidence of CRC in the general Turkish population. These figures are similar to those observed in Asian research but much lower than those reported by Western countries.²⁹

Limitations

The current study has several limitations that should be acknowledged. First, despite the long follow-up period, the number of patients who developed CRC was low, which may limit the generalizability of the findings and the power to detect significant differences in risk factors between the CRC and non-CRC groups. Second, the clinic where the study was conducted is an experienced referral center for inflammatory bowel diseases and follows an effective approach in applying immunomodulators and biological agents to patients with ongoing mucosal inflammation. This approach may not

be representative of the general practice in other clinics throughout the country, where there may be hesitation about initiating immunomodulators and biological agents. Consequently, the incidence of CRC developing on the basis of UC in Turkey may be higher than what was observed in the current study. Third, the study's retrospective design is another limitation that should be considered when interpreting the results, as it may introduce selection and information biases.

Furthermore, the study did not assess the impact of disease severity, duration of inflammation, or the extent of mucosal healing on the risk of CRC development. These factors have been shown to influence the risk of CRC in UC patients and should be considered in future studies. Additionally, the study did not evaluate the adherence to surveillance colonoscopy guidelines or the quality of colonoscopies performed, which are essential factors in the early detection and prevention of CRC in UC patients.

Despite these limitations, the study also has notable strengths. The regular recording of patients' data by experienced gastroenterologists ensures the reliability and accuracy of the information collected. Moreover, the application of an accelerated step-up treatment approach for the effective treatment of mucosal inflammation may have contributed to the low incidence of CRC in the patients included in the study. The long follow-up period of 30 years is another strength, as it allows for the assessment of long-term outcomes and risk factors associated with CRC development in UC patients.

CONCLUSION

In conclusion, this study found a CRC frequency of 0.6% among UC patients in the non-endemic area, which is significantly lower than the rates reported in previous studies of UC cases. This lower incidence may be attributed to several factors, including the non-endemic nature of the region for sporadic CRC and inflammatory bowel disease, as well as certain environmental and racial factors specific to the non-endemic area.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Ankara Bilkent City Hospital Scientific Researches Ethics Committee (Date: 25.01.2023, Decision No: E1/23/3219).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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